PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 49/00 — A1

(11) International Publication Number: **WO 97/02842**

(43) International Publication Date: 30 January 1997 (30.01.97)

(21) International Application Number: PCT/DK96/00315

(22) International Filing Date: 10 July 1996 (10.07.96)

(30) Priority Data:
0810/95 11 July 1995 (11.07.95) DK

(71)(72) Applicant and Inventor: THOMSEN, Henrik, S. [DK/DK]; Ved Ørehøj 6, DK-2900 Hellerup (DK).

(74) Agent: HOFMAN-BANG & BOUTARD, LEHMANN REE A/S; Adelgade 15, DK-1304 Copenhagen K (DK).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: MR CONTRAST AGENT

(57) Abstract

A composition for use as a contrast medium being particularly suitable for imaging of the stomach, liver, bile duct and gall bladder, said composition comprising as an active ingredient a physiologically acceptable manganese compound and an uptake promoter, wherein the uptake promoter comprises a physiologically acceptable reducing compound containing a physiologically acceptable amino acid or a salt thereof, and/or vitamin D.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgystan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
FI	Finland	ML	Mali	US	United States of America
FR	France	MN	Mongolia	UZ	Uzbekistan
GA	Gabon	MR	Mauritania	VN	Viet Nam

MR contrast agent

The present invention relates to improvements on and relating to magnetic resonance imaging (MRI) and in particular to compositions for use as or in the preparation of MRI contrast media for imaging of the stomach, liver, bile duct and gall bladder. The MRI contrast media may also be used for imaging the pancreas and the heart.

MRI is now well established as a medical diagnostic tool. The ability of the technique to generate high quality images and to differentiate between soft tissues without requiring the patient to be exposed to ionizing radiation has contributed to this success.

Although MRI can be performed without using added contrast media, it has been found that substances which affect the nuclear spin reequilibration of the nuclei (hereinafter the "imaging nuclei" - generally water protons in body fluids and tissues) responsible for the magnetic resonance (MR) signals from which the images are generated may be used to enhance image contrast and, accordingly, in recent years, many such materials have been suggested as MRI contrast agents.

The enhanced contrast obtained with the use of contrast agents enables particular organs or tissues to be visualised more clearly by increasing or by decreasing the signal level of the particular organ or tissue relative to that of its surroundings. Contrast agents raising the signal level of the target site relative to that of its surroundings are termed "positive" contrast agents whilst those lowering the signal level relative to surroundings are termed "negative" contrast agents.

The majority of materials now being proposed as MRI contrast media achieve a contrast effect because they contain paramagnetic, superparamagnetic or ferromagnetic species.

For ferromagnetic and superparamagnetic contrast agents, which are negative MRI contrast agents, the enhanced image contrast derives primarily from the reduction in the spin reequilibration parameter known as arising from the effect on the imaging nuclei of the fields generated by the ferromagnetic or superparamagnetic particles.

Paramagnetic contrast agents on the other hand may be either positive or negative MRI contrast agents. The effect of paramagnetic substances on magnetic resonance signal intensities is dependent on many factors, the most important of which are the concentration of the paramagnetic substances at the imaged site, the nature of the paramagnetic substance itself, and the pulse sequence and magnetic field strength used in the imaging routine.

Generally, however, paramagnetic contrast agents are positive MRI contrast agents at low concentrations where their T_1 lowering effect dominates, and negative MRI contrast agents at higher concentrations where their T_2 lowering effect is dominant. In either event, the relaxation time reduction results from the effect on the imaging nuclei of the magnetic fields generated by the paramagnetic centres.

The use of paramagnetic, ferromagnetic and superparamagnetic materials as MRI contrast agents has been widely advocated, and broad ranges of suitable materials have been suggested in the literature.

An example of a physiologically acceptable paramagnetic material known for use as an MRI contrast agent is manganese ion, which may conveniently be used in the form of its salts, chelates or other complexes. Indeed, even at very low intravenuos dosages (about 5-10 µmol/kg body weight) manganese ions have been found to be particularly effective as a contrast agent for imaging of the liver.

However, manganese, when administered intravenously as a contrast agent, may be teratogenic at clinical dosages. Administered intravenously, manganese is also known to interfere with the normal functioning of the heart by replacement of calcium in the calcium pump of the heart. It has been reported that dosages of manganese injected into rats in excess of 0,1 mmol/kg body weight were often lethal.

In order to reduce the direct effect on the heart, oral administration has been proposed. This ensures passage of the contrast agent through the liver before going to the heart and thereby decreasing the possibility of a heart attack.

Oral administration of $MnCl_2$ as a liver imaging MR contrast agent has been proposed, and orally administered $MnCl_2$ has not been found to be teratogenic. However, the adsorption of $MnCl_2$ through the gut is poor, and as a result the dosage required for clinical efficacy is of the order 100-1000 µmol/kg body weight. In the event of damage to the gut resulting in increased uptake, such a high dosage level still has the potential for causing undesired adverse effects, e.g. cardiac effects.

The toxicity of manganese ions precludes their administration in amounts large enough to be useful in MRI.

It has been found that paramagnetic chelates are less toxic than the free ions, but the chelation will prevent or reduce the enhancement of binding of paramagnetics with tissues. This means that a greater amount of the chelate will be needed to produce the same effect as the free ions.

EP A2 308 983 describes a MR imaging composition containing manganese(II) coordination compounds and their use in MRI. The invention is in particular directed to manganese(II) coordination complexes with water-soluble amino acids, to MR imaging compositions containing these complexes, and to their use in MRI. These compounds have proven to be more safe and provide the same relaxivity as manganese salts. The non-chelated compounds do not affect the binding of manganese to body tissue and blood components, and particularly heart and liver tissue, and reduce the toxicity. Solutions of the compound can be administered rectally, orally or parenterally, preferably parenterally.

Although it is stated that these solutions may be administered orally, none of the examples show what oral dosage is neccessary to achieve a measuarable MR image. Only injected dosages have been reported, and these dosages are not suffient for oral administration.

We have now surprisingly found that gastrointestinal tract manganese contrast agents suitable for imaging of the liver may be produced by the incorporation of an uptake promoter capable of enhancing manganese transport across the membranes of the gastrointestinal tract.

Compounds which have been found to be suitable for use as uptake promoters include amino acids, vitamin D or a combination thereof.

Thus, viewed from one aspect the present invention provides a contrast medium composition comprising a physiologically acceptable manganese compound, an uptake promoter and a physiologically acceptable carrier or excipient, wherein the uptake promoter comprises an amino acid and/or vitamin D.

The contrast medium composition according to the invention may comprise a manganese compound together with a mixture of several uptake promoters, i.e. a mixture of several amino acids and/or vitamin D.

The manganese compound, which preferably is soluble in gastrointestinal fluid, may for example be a salt, a chelate or another complex, or may be a mixture of different salts, chelates and/or complexes. Particularly preferred are metal chelates and salts in which the manganese is present as Mn(II) rather than Mn(III), since the former has a higher magnetic moment and thus is more effective as a MR contrast agent. Suitable salts are salts of inorganic anions, e.g. chlorides, bromides, iodies, flourides, sulfates, phosphates, preferably chlorides and salts of organic anions.

Another manganese source is manganese containing foodstuff such as blueberry juice, green tea and nuts. Also these manganese sources may be combined with an uptake promoter according to the invention.

The reducing nature of the uptake promoter is important since normal uptake of manganese by the gut tends to favour Mn(II) rather than Mn(III).

Examples of amino acids which have been found to be effective as uptake promoters in the compositions of the invention include all the native amino acids, i.e. alanine,

valine, leucine, tryptophan, methionine, isoleucine, proline, phenylalanine, serine, glycine, threonine, cysteine, aspargine, glutamine, tyrosine, aspartic acid, glutamic acid, arginine, lycine and histidine. Particularly preferred as an uptake promoter in the composition of the invention are the amino acids L-aspartic acid and L-alanine.

The preferred vitamin is vitamin D_3, but all subgroups of vitamin D are suitable. Vitamin D is a fat soluble vitamin and soluble in organic solvents. A preferred solvent is polyethylene glycol.

The increase in the uptake of manganese for various uptake promoters is demonstrated in the figures, which are MR images of the liver of rats after administering the contrast medium composition orally.

Using the compositions of the invention, the liver can be effectively MR imaged with a significant reduction in the dosage of manganese otherwise required when administered orally.

The figures illustrate cross section images of the body of rats in the liver region. The groups are defined in the example.

Figure 1 illustrates images from rats of group 2 (top), group 5 (mid left), group 1 (control) (mid right), and group 7 (bottom).

The signal intensities were as follows:
Group 2: Average signal intensity 112
Group 5: Average signal intensity 134
Group 1: Average signal intensity 98
Group 7: Average signal intensity 121

Figure 2 illustrates images from rats of group 4 (top), group 3 (mid left), group 1 (control) (mid right), and group 7 (bottom).

The signal intensities were as follows:
Group 4: Average signal intensity 127
Group 3: Average signal intensity 139
Group 1: Average signal intensity 106
Group 7: Average signal intensity 129

Figure 3 illustrates images from rats of group 7 (top), group 4 (mid left), group 1 (control) (mid right), and group 2 (bottom).

The signal intensities were as follows:
Group 7: Average signal intensity 146
Group 4: Average signal intensity 135
Group 1: Average signal intensity 109
Group 2: Average signal intensity 101

In the composition according to the invention, the preferred molar ratio of manganese to uptake promoter is from 1:0,2 to 1:50, preferably 1:1 to 1:20, more preferably 1:3 to 1:6, and most preferably about 1:5.

If desired, the uptake promoter may be present in whole or in part as the counterion to the manganese ions.

The composition according to the invention may be used to achieve a so-called "double contrast effect" by increasing the signal level from the liver whilst at the same time decreasing that from the surrounding tissues, in particular from the gut. Such an effect enables yet further enhancement of the image of the liver.

In a particularly preferred embodiment, the composition of the invention may be used in combination with a second contrast agent having either a positive or negative contrast effect. Preferably, the compositions of the invention are used in combination with a second contrast agent having an opposing contrast effect. This results in a "double contrast effect" enabling visualisation and margin definition of the liver to be particularly enhanced.

As mentioned above, paramagnetic materials, such as manganese ions, may act as either positive or negative MRI contrast agents depending upon a number of factors, including the concentration of the ions at the imaging site and the magnetic field strength used in the imaging procedure. At the concentrations of manganese comtemplated for use in the compositions of the invention, the manganese-containing contrast agent will in general function as a positive contrast agent. The second contrast agent is therefore conveniently negative contrast agent and may be any negative MRI contrast agent suitable for oral administration.

Examples of contrast agents for use in combination with the composition of the invention include iron (Fe), gadolinium (Gd) and dyprosium (Dy).

When using the composition of the invention to achieve a double contrast effect, it is particularly preferable to incorporate a viscosity enhancing agent which attains its full viscosity enhancing effect only after administration of the contrast medium. The contrast medium is thus able to be ingested in a relatively tolerable form while yet developing the desired viscosity at or during passage towards the site which is to be imaged.

The compositions of the invention are particularly suited to use, if required, after dispersion in aqueous media, for imaging of the liver. For such a purpose the composition may be administered into the gastrointestinal tract orally, rectally or via a stomach tube.

Thus, viewed from a further aspect the present invention provides a method of generating a magnetic resonance image of a human or non-human, preferably mammalian, animal body, which method comprises administering into the gastrointestinal tract of said body an effective amount of a contrast medium comprising a physiologically acceptable manganese compound and a physiologically acceptable reducing compound containing a physiologically acceptable amino acid or a salt thereof, and/or vitamin D, and generating a magnetic resonance image of the liver and the gastrointestinal tract of said body.

In a further embodiment the invention provides a method of generating a magnetic resonance image of a human or non-human animal body, which method comprises administering into the gastrointestinal tract of said body an effective amount af a composition comprising: (a) a first contrast agent comprising a physiologically acceptable manganese compound and a physiologically acceptable reducing compound containing a physiologically acceptable amino acid or a salt thereof, and/or vitamin D, together with (b) a second contrast agent and generating a magnetic resonance image of the liver and abdomen of said body.

It is possible to formulate the contrast medium immediately or shortly prior to administration by mixing the uptake promoter with the manganese species. Thus, in a further aspect the invention also provides a MRI contrast agent kit comprising in a first container a physiologically acceptable manganese compound, and in a second container a

physiologically acceptable reducing compound containing an amino acid or a salt thereof, and/or vitamin D.

In a further embodiment of the invention the first container comprises a first contrast agent comprising a physiologically acceptable manganese compound together with a physiologically acceptable reducing compound containing an amino acid or a salt thereof, and/or vitamin D, and the second container comprises a second contrast agent.

The contrast agent composition of the invention may of course include components other than the uptake promoter, the manganese compound, for example conventional pharmaceutical formulation aids, such as wetting agents, buffers, disintegrants, binders, fillers, flavouring agents and liquid carrier media, such as sterile water, water/ethanol etc.

For oral administration, the pH of the composition is preferably in the acid range, e.g. 2 to 7, and while the uptake promoter may itself serve to yield a composition with this pH, buffers or pH adjusting agents may be used.

The contrast media may be formulated in conventional pharmaceutical administration forms, such as tablets, capsules, powders, solutions, dispersions, syrups, suppositories etc. When the contrast media can be administered orally, a patient can administer the contrast media himself 2 to 3 hours before being scanned. The patient is not obliged to stay in the hospital for several hours before being scanned.

The preferred dosage of the composition according to the present invention will vary according to a number of factors, such as the administration route, the age, weight and species of the subject, and the particular uptake

promoter used. Conveniently, the dosage of manganese will be in the range from 5 to 500 µmol/kg body weight, preferably from 5 to 150 µmol/kg body weight, more preferably from 10 to 100 µmol/kg body weight, while the dosage of the uptake promoter will be in the range from 5 µmol to 1 mmol/kg body weight, preferably from 25 µmol to 0,5 mmol/kg body weight.

The following example illustrates the effectiveness of the uptake of manganese for various uptake promoters.

The studies were carried out on seven groups of rats with six rats in each group. MRI examination was done with a quadrature knee-coil in a 0,1 T MRI unit. Each scanning included four rats, and the examination was carried out three hours after the contrast medium was administered to the rats. If experiments are carried out with a higher tesla unit, e.g. 1,0 or 1,5 T, a larger increase in signal intensity can be expected.

After a 12 hour diet various contrast medium compositions were orally administered to the various groups of rats. The contrats medium was administered to the stomach of the rats via a catheter. Three hours after administration the rats were killed and placed in a tube. Thereafter the rats were scanned.

The following non-limiting example illustrates various compositions administered to various groups of rats. The results of the scannings are illustrated in the figures.

In the example the units µmol/kg and mg/kg refer to µmol/kg body weight and mg/kg body weight

Example A

To group 1 (control) no contrast medium was administered.

To group 2 100 µmol/kg (19,8 mg/kg) manganese(II)chloride tetrahydrate were administered

To group 3 100 µmol/kg (19,8 mg/kg) manganese(II)chloride tetrahydrate and 300 µmol/kg (42 mg/kg) L-aspartic acid were administered.

To group 4 100 µmol/kg (19,8 mg/kg) manganese(II)chloride tetrahydrate, 300 µmol/kg (42 mg/kg) L-aspartic acid and 0,1 mg/kg vitamin D_3(10 µg/ml) were administered.

To group 5 100 µmol/kg (19,8 mg/kg) manganese(II)chloride tetrahydrate and 300 µmol/kg (25 mg/kg) L-alanine were administered.

To group 6 100 µmol/kg (19,8 mg/kg) manganese(II)chloride tetrahydrate, 300 µmol/kg (25 mg/kg) L-alanine and 0,1 mg/kg vitamin D_3(10 µg/ml) were administered.

To group 7 100 µmol/kg (19,8 mg/kg) and 0,1 mg/kg vitamin D 3 (10 µg/ml) were administered.

Now referring to figur 1 it can be seen that the average signal intensity of the liver is substantially increased after administration orally of manganese(II)chloride tetrahydrate and L-alanine or manganese(II)chloride tetrahydrate and vitamin D_3, respectively.

Referring to figur 2 it can be seen that the average signal intensity of the liver is substantially increased after administration orally of manganese(II)chloride tetrahydrate

and L-aspartic acid and vitamin D_3, L-aspartic acid or vitamin D_3, respectively.

Referring to figur 3 it can be seen that the average signal intensity of the liver is substantially increased after administration of manganese(II)chloride tetrahydrate and vitamin D_3 or manganese(II)chloride tetrahydrate and L-aspartic acid and vitamin D_3, respectively.

The following example illustrates preferred compositions administered to a human depending on the body weight.

Example B

Tabel

Body weight (kg)	Manganese(II) chloride tetrahydrate (g)	L-alanine (g)
60	1,188	1,500
70	1,386	1,750
80	1,568	2,000
90	1,782	2,250
100	1,980	2,500

Before being administered to the human the manganese(II) chloride tetrahydrate and L-alanine are dissolved in 250 ml of water.

Claims

1. A contrast medium composition comprising as an active ingredient a physiologically acceptable manganese compound and an uptake promoter, wherein the uptake promoter comprises a physiologically acceptable reducing compound containing a physiologically acceptable amino acid or a salt thereof, and/or vitamin D.

2. A composition as claimed in claim 1, wherein the uptake promoter comprises one or more of the compounds defined in claim 1.

3. A composition as claimed in claim 1 or claim 2, wherein the manganese compound is a salt, a chelate or another complex in which the manganese is present as Mn(II).

4. A composition as claimed in any one of the claims 1 to 3, wherein the amino acid is an α- or β-amino acid.

5. A composition as claimed in claim 4, wherein the amino acid is alanine, valine, leucine, tryptophan, methionine, isoleucine, proline, phenylalanine, serine, glycine, threonine, cysteine, aspargine, glutamine, tyrosine, aspartic acid, glutamic acid, arginine, lysine and histidine, preferably L-alanine or L-aspartic acid.

6. A composition as claimed in claim 4 or claim 5 further comprising vitamin D.

7. A composition as claimed in claim 6, wherein the vitamin is any subgroup of vitamin D, preferably vitamin D_3.

8. A composition as claimed in any one of claims 1 to 3, wherein the uptake promoter is vitamin D.

9. A composition as claimed in claim 8, wherein the vitamin is any subgroup of vitamin D, preferably vitamin D_3

10. A composition as claimed in any of the preceding claims, wherein the uptake promoter is present in whole or in part as the counterion to the manganese ions.

11. A composition as claimed in any of the preceding claims further comprising a physiologically acceptable carrier or excipient.

12. A MRI contrast agent kit comprising in a first container a physiologically acceptable manganese compound, and in a second container a physiologically acceptable reducing compound containing a physiologically acceptable amino acid or a salt thereof, and/or vitamin D.

13. A contrast medium composition comprising as an active ingredient a manganese containing foodstuff, such as blueberry juice, green tea, and nuts, and an uptake promoter, wherein the uptake promoter comprises a physiologically acceptable reducing compound containing a physiologically acceptable amino acid or a salt thereof and/or vitamin D.

14. A composition as claimed in claim 13, wherein the uptake promoter comprises one or more of the compounds defined in claim 13.

15. A composition as claimed in claim 13 or claim 14, wherein the manganese compound is a salt, a chelate or another complex in which the manganese is present as Mn(II).

16. A composition as claimed in any one of the claims 13 to 15, wherein the amino acid is an α- or β-amino acid.

17. A composition as claimed in claim 16, wherein the acid is alanine, valine, leucine, tryptophan, methionine, isoleucine, proline, phenylalanine, serine, glycine, threonine, cysteine, aspargine, glutamine, tyrosine, aspartic acid, glutamic acid, arginine, lycine and histidine, preferably L-alanine or L-aspartic acid.

18. A composition as claimed in claim 16 or claim 17 further comprising vitamin D.

19. A composition as claimed in claim 18, wherein the vitamin is any subgroup of vitamin D, preferably vitamin D_3 .

20. A composition as claimed in any one of claims 13 to 15, wherein the uptake promoter is vitamin D.

21. A composition as claimed in claim 20, wherein the vitamin is any subgroup of vitamin D, preferably vitamin D_3 .

22. A composition as claimed in any of the claims 13 to 21, wherein the uptake promoter is present in whole or in part as the counterion to the manganese ions.

23. A composition as claimed in any of the claims 13 to 22 further comprising a physiologically acceptable carrier or excipient.

24. A method of generating a magnetic resonance image of a human or non-human animal body, which method comprises administering into the gastrointestinal tract of said body a contrast medium comprising a physiologically acceptable manganese compound and a physiologically acceptable

reducing compound containing a physiologically acceptable amino acid or a salt thereof, and/or vitamin D, and generating a magnetic resonance image of the liver and abdomen of said body.

25. A contrast medium composition comprising:
- a composition as claimed in any one of the claims 1 to 11 or 13 to 23, together with
- a second contrast agent.

26. A composition as claimed in claim 25, wherein the second contrast agent has an opposing contrast effect to said first contrast agent.

27. A composition as claimed in claim 25 or claim 26, wherein the second contrast agent has a negative contrast effect.

28. A composition as claimed in claim 25 or claim 26, wherein the second contrast agent has a positive contrast effect.

29. A composition as claimed in claim 25 or claim 26, wherein the second contrast agent comprises a particulate ferromagnetic or superparamagnetic material.

30. A composition as claimed in claim 25 or claim 26, wherein the second contrast agent comprises Fe, Gd or Dy ions bound to a polymeric matrix.

31. A method of generating a magnetic resonance image of a human or non-human body, which method comprises administering into the gastroinstinal tract of said body an effective amount of a composition as defined in claim 25 and generating a magnetic resonance image of the liver and abdomen of said body.

32. A MRI contrast agent kit comprising in a first container a first contrast agent comprising a physiologically acceptable manganese compound, a physiologically acceptable reducing compound containing a physiologiaclly acceptable amino acid or a salt thereof, and/or vitamin D, and in a second container a second contrast agent as defined in claim 29 or claim 30.

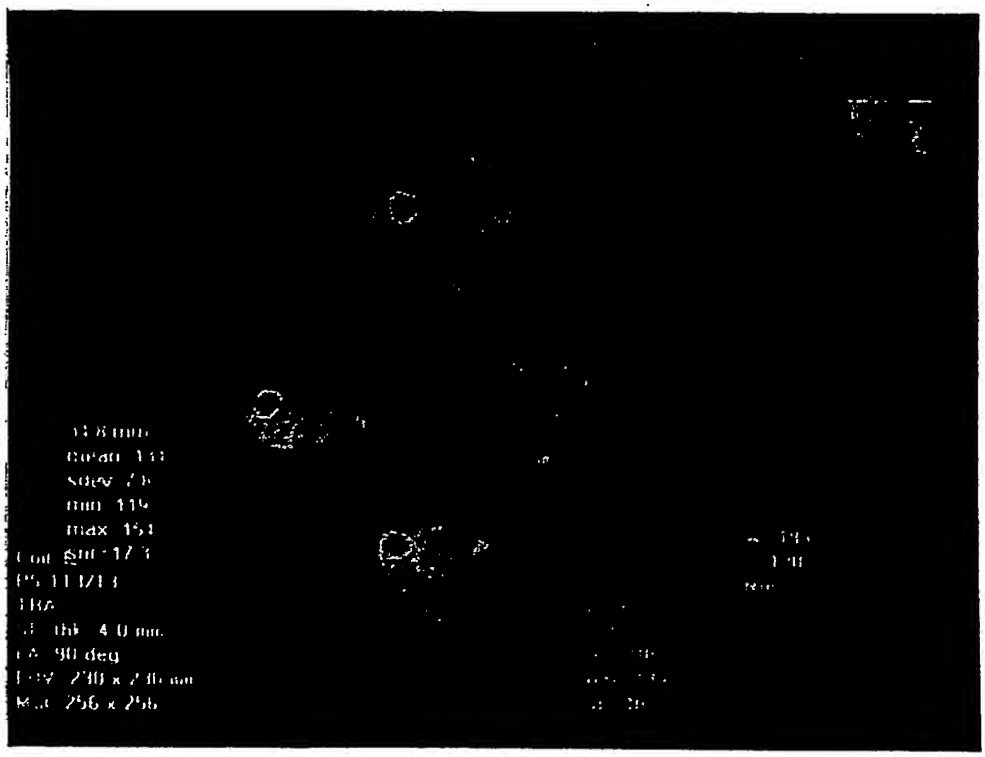

FIG. 1

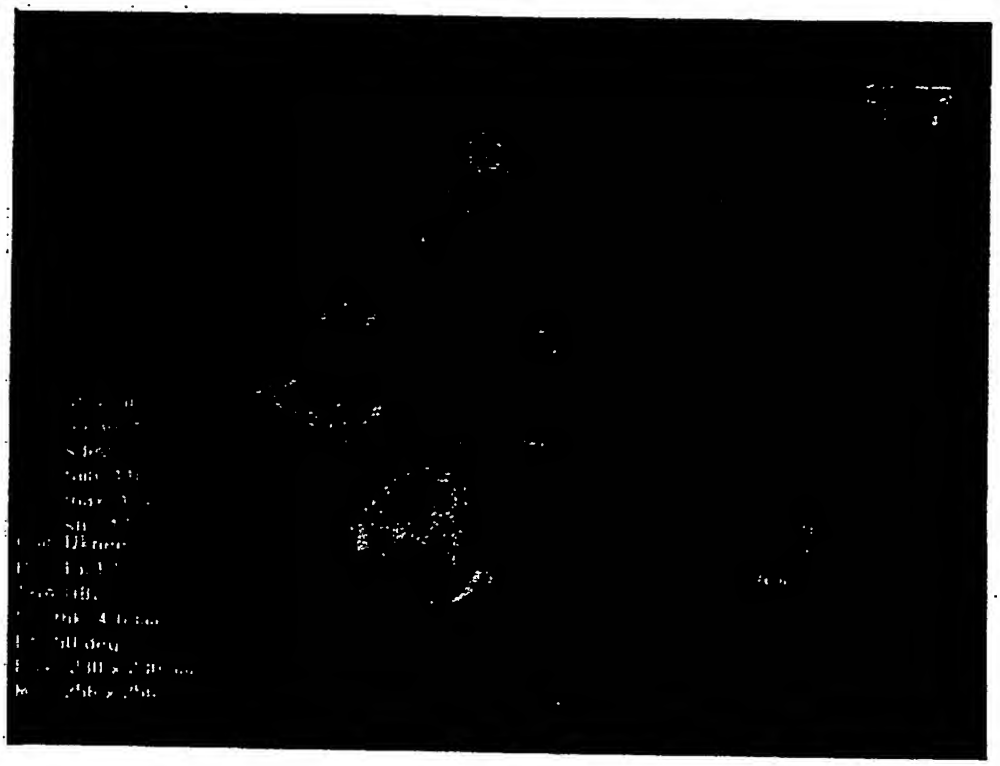

FIG. 2

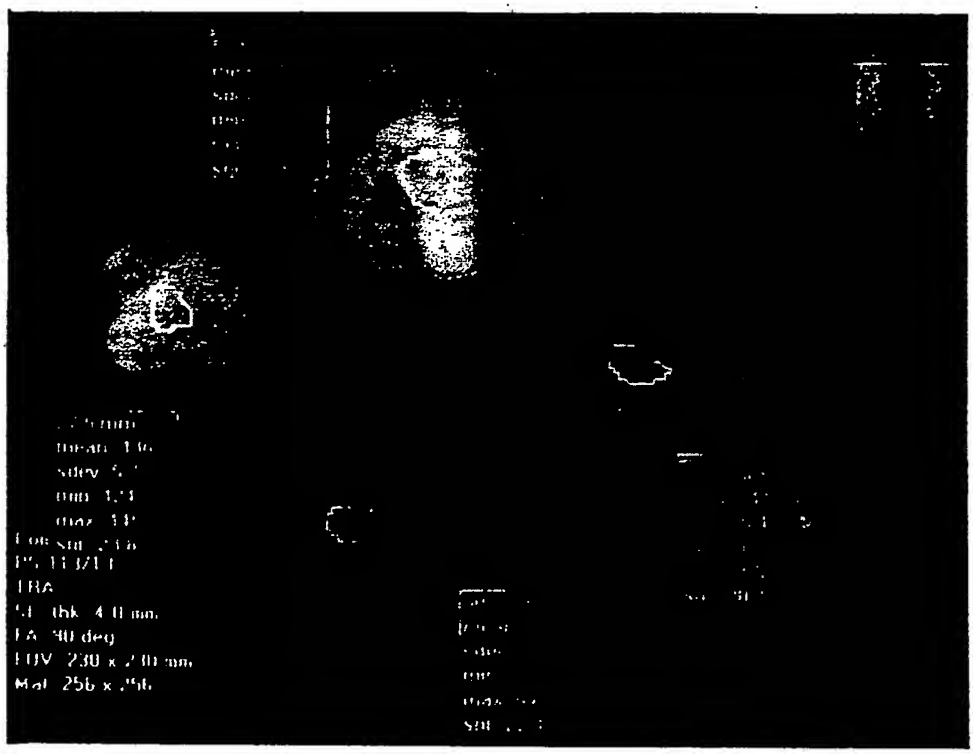

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00315

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 49/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9605867 A2 (NYCOMED IMAGING A/S), 29 February 1996 (29.02.96) --	1-32
Y	EP 0308983 A2 (SALUTAR, INC.), 29 March 1989 (29.03.89), the claims --	1-7,10-19, 22-24
Y	WO 9517910 A2 (BRACCO S.P.A.ET AL), 6 July 1995 (06.07.95), the claims --	1-7,10-19, 22-24
Y	US 5292729 A (HARVEY H. ASHMEAD), 8 March 1994 (08.03.94), examples 12, 14, 15, the description, column 3, line 15-24 --	1-7,10-19, 22-24

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 October 1996	17 -10- 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00315

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 8704622 A1 (ALBION LABORATORIES, INC.), 13 August 1987 (13.08.87), page 7; page 15, examples 13, 14, 28, the claims -- --------	1-7,10-19, 22-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00315

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 24,31
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 24, 31 are directed to a treatment/diagnosis of the human/animal body, the search has been carried out, based on the alleged effects of the compound/composition (Rule 39.1(iv)).

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Three different inventions were stated. For further information please see continuation sheet!

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

1 Claims 4-7, 16-19, and parts of claims 1-3, 10-15 and 22-24: a contrast medium composition, in which the contrast agent is containing a manganese compound, and as uptake promotor an amino acid, its use in magnetic resonance imaging, and a kit for preparing the contrast medium composition.

2 Claims 8-9, 20-21, and parts of claims 1-3, 10-15 and 22-24: a contrast medium composition, in which the contrast agent is containing a manganese compound, and as uptake promotor vitamin D, its use in magnetic resonance imaging, and a kit for preparing the contrast medium composition.

3 Claims 25-32: a contrast medium composition containing a manganese compound, an uptake promotor, together with a second contrast agent, its use in magnetic resonance imaging, and a kit for preparing the contrast medium composition.

The problem underlying the present application is, in its broadest form, the provision of safer contrast agents for NMR imaging, containing manganese ions.

As a solution to this problem, different uptake promotors are used.

The special technical feature, linking these solutions together, is the use of an uptake promotor for manganese ions.

This use is already known in the prior art. US,A, 5292729 and WO,A1, 87/04622 shows that the uptake of Mn in the G I-system are affekted by amino acids.
Moreover NMR-compositions containing bothmanganese and amino acid promotors have been described before: see e.g. EP, A2, 0308983 and WO, A2, 95/17910.

For this reason, the special technical feature mentioned above can no longer be accepted as technical feature linking the different inventions together. Therefore, the present application lacks unity of invention.

INTERNATIONAL SEARCH REPORT

Information on patent family members

05/09/96

International application No.
PCT/DK 96/00315

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A2- 9605867	29/02/96	AU-A- 3262095	14/03/96
		GB-D- 9416767	00/00/00
		GB-D- 9416768	00/00/00
EP-A2- 0308983	29/03/89	AU-A- 2278988	06/04/89
		JP-A- 1259850	17/10/89
WO-A2- 9517910	06/07/95	IT-D- MI932728	00/00/00
US-A- 5292729	08/03/94	AU-A- 4790193	15/03/94
		CA-A- 2142358	03/03/94
		EP-A- 0662830	19/07/95
		JP-T- 8502729	26/03/96
		WO-A- 9404141	03/03/94
WO-A1- 8704622	13/08/87	AU-B- 599637	26/07/90
		AU-A- 7038587	25/08/87
		CA-A- 1293444	24/12/91
		DE-A,T- 3787061	23/09/93
		EP-A,B- 0262178	06/04/88
		SE-T3- 0262178	
		JP-T- 63502749	13/10/88
		US-A- 4863898	05/09/89